



March 29, 2021

Dear Huntington's disease community:

We have a disappointing update to share regarding our Huntington's disease (HD) clinical candidates being studied in the PRECISION-HD1 (WVE-120101) and PRECISION-HD2 (WVE-120102) Phase 1b/2a clinical trials. After reviewing data from the PRECISION-HD2 trial, we have made the difficult decision to discontinue development of WVE-120102. Complete data from the PRECISION-HD1 trial are not yet available, but the data we have reviewed to date are similar to those in the PRECISION-HD2 trial, and we will also discontinue development of WVE-120101.

Trial results and what it means.

The results from the PRECISION-HD2 trial showed no significant change in mutant huntingtin (mHTT) protein in adults with HD treated with WVE-120102 relative to those treated with placebo, and no evidence of a dose response across the dose levels tested. WVE-120102 was generally safe and well-tolerated at lower doses; however, there were safety events experienced at the highest dose which led to participants discontinuing the trial. Unfortunately, the results from the trial, as well as from models that project likely results we might see with a higher dose, do not support further development of WVE-120102.

Similarly, the results of the PRECISION-HD1 trial showed no significant change in mHTT protein in adults with HD treated with WVE-120101 relative to those treated with placebo.

Participants currently enrolled in the PRECISION-HD open label extension trials will have a final follow-up visit but will not receive further doses.

For a more detailed summary of these trials, please see our press release [here](#).

What happens next?

Our work to advance research in HD continues with our third HD clinical candidate, WVE-003. WVE-003 is an investigational stereopure antisense oligonucleotide (ASO) designed to selectively reduce mHTT protein while leaving healthy, or wild-type, huntingtin (wtHTT) protein relatively unchanged. WVE-003 is designed differently from our first two HD clinical candidates, WVE-120102 and WVE-120101, and incorporates novel chemical modifications. The promising preclinical data we have seen thus far with WVE-003 give us confidence in this novel program. We expect to initiate dosing in our Phase 1b/2a trial of WVE-003 in 2021.

We will also share data from both the PRECISION-HD1 and PRECISION-HD2 clinical trials at upcoming advocacy and medical meetings this year.

Our gratitude

This is not the update we were hoping to provide, and we recognize this has already been an extremely challenging month for the HD community. However, we have had the privilege of speaking and working with many of you over the past few years and we know firsthand of the strength, perseverance, and resiliency of this community. We are committed to learning all we can from these trials and have already applied lessons learned to the clinical development of WVE-003.

We would like to extend our heartfelt thanks to the courageous study participants and their families, as well as to our research partners and investigators. We look forward to continuing our collaboration to advance promising research in HD and will share more information on the WVE-003 clinical trial later this year.

Sincerely,

A handwritten signature in black ink that reads "Jeffrey Smith". The signature is written in a cursive, flowing style.

Jeffrey Smith, Senior Director, Head, Patient Advocacy
On behalf of the team at Wave Life Sciences

Questions and Answers

When will the full results from PRECISION-HD2 and PRECISION-HD1 trials be shared?

We will share data from both the PRECISION-HD1 and PRECISION-HD2 clinical trials at upcoming advocacy and medical meetings this year. The timing and venue will be dependent on completion of a more detailed data analysis for both trials.

When will the clinical trial for WVE-003 start and how do I learn more about participating in the trial?

We expect that the initial clinical trial for WVE-003 will start enrolling and dosing participants in 2021. Please speak with your health care provider to help determine whether an upcoming clinical trial is an option for you. Your clinical team will help you determine your eligibility for the trial and will help to connect you to a clinic that is participating in the trial. Clinical sites and trial investigators are ultimately responsible for screening participants to determine eligibility and enrolling participants into the trial.

What gives you the confidence to go forward with a trial for WVE-003 given the results seen with WVE-120102 and WVE-120101?

WVE-003 is an investigational clinical candidate with novel chemical modifications, so it is different from WVE-120102 and WVE-120101. The preclinical data we have seen for WVE-003 give us confidence to initiate a clinical trial to evaluate safety, tolerability, and biomarkers such as mHTT and wtHTT.

Will individuals participating in either PRECISION-HD2 or PRECISION-HD1 be able to be screened in the WVE-003 trial?

Yes. Participants from the PRECISION-HD trials will be offered the opportunity to undergo screening for potential enrollment in the trial of WVE-003.

Who is eligible for the WVE-003 trial?

To be eligible for the WVE-003 trial, potential participants will be screened to confirm an HD diagnosis and the presence of a single nucleotide polymorphism (SNP) that is targeted by WVE-003 (SNP3). SNPs are normal variations in DNA, and the presence of SNP3 enables WVE-003 to specifically target mHTT. It is estimated that approximately 40% of adults with HD carry SNP3 in association with the HD mutation. Other eligibility criteria will also need to be met.